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CONFIDENTIAL

PROCESS FOR PRODUCING WET RIBAVIRIN PELLETS

BACKGROUND OF THE INVENTION

1. Field Of The Invention

The present invention relates to a process for making oral pharmaceutical dosages of ribavirin. More specifically, the drug ribavirin is a synthetic nucleoside analog with broad spectrum antiviral activity. Ribavirin is one of a combination of drugs being administered to patients with Hepatitis C and other viral infections.

Ribavirin is currently manufactured, among other methods, using a process commonly called dry compaction. Dry compaction utilizes high pressure to form a ribbon of ribavirin that is subsequently reduced to a free flowing powder by milling. The undesirable side effects of manufacturing ribavirin by dry compaction include the creation of excessive dust, a potential health hazard, as well as the risk that high pressure, which can produce high heat, could produce polymorphic forms. Different polymorphs or combinations of polymorphs are undesirable because they can sometimes change the manner in which the active drug moiety is absorbed.

The present invention describes a method for manufacturing ribavirin using a wet granulation process. This process forms a free flowing ribavirin by mixing ribavirin with a wetting agent and various excipients to form a granulation that can be extruded and spheronized, producing a pellet. This process is not only an alternative method for producing ribavirin, but also offers several advantages over the dry compaction process. One advantage of wet granulation is that significantly less dust is produced, which is important from a health and safety standpoint. Another advantage of the present invention is that wet granulation allows for greater control of dissolution rates. In addition, this wet granulation method results in the

ribavirin having better flow characteristics, enabling faster encapsulation and lower weight variations. Finally, because there is little heat or excessive pressure, the wet granulation method lowers the risk of creating polymorphs and, therefore, allows for greater uniformity of the crystalline structure.

2. Description Of The Prior Art

It is well known in the art that a raw drug often is unsuitable for medicinal purposes because the raw drug has undesirable dissolution profiles and cannot be efficiently encapsulated because of poor flow qualities. For efficient encapsulation, proper flow is vital to producing a uniform, quality pharmaceutical product for a variety of reasons, including that these factors can affect how much active drug is absorbed and when it is absorbed into the human body.

Excipients are often added to raw drugs in order to create a mixture having improved flow, compaction, or disintegration characteristics. These excipients can add various qualities either to the end product or to some stage of the manufacturing process. Common excipients include disintegrants, lubricants, fillers, binders and wetting agents. Disintegrants absorb water quickly when the dosage form reaches the alimentary canal. Lubricants help with mold release and flow. Fillers provide bulk and, along with binders and wetting agents, add adhesion to the mixture. However, some formulas produce a finished dosage form that is too large or results in disintegration rates which could be slower or faster than is optimal.

The following three methods are commonly used to mix excipients with raw drugs to produce pharmaceutical capsules: (1) direct blend, (2) dry compaction, and (3) wet granulation. In the direct blend process, drugs and selected excipients are added to a blender and mixed in the dry state to produce a uniform distribution of the active drug. This direct blend method requires an active drug with acceptable flow characteristics. In the dry compaction process, drugs and selected excipients are mixed and then compacted into a ribbon and milled to a uniform particle size. This operation often generates heat. The result is a free flowing powder

that can be encapsulated. Finally, in the wet granulation process, the drugs are mixed either in their liquid form or with a wetting agent to produce a wet mass that can be further processed to produce a free flowing material, which in turn can be encapsulated.

Heretofore, there have been no references in the prior art that demonstrate the successful use of the wet granulation process to manufacture ribavirin capsules. Rather ribavirin is presently made using a dry compaction process as shown in Patent Nos. 6,051,252, 5,196,594 and 5,914,128. Each of Patent Nos. 6,051,252, 5,196,594 and 5,914,128 describes a method of producing dosages of ribavirin using high pressures which could generate high temperatures. Specifically, Patent Nos. 6,051,252 and 5,914,128 both describe the use of compressing forces that range from 50 to 75 kilonewtons of force.

Although the most common pharmaceutical dosage of ribavirin is 200mg, other dosages could be manufactured.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an alternative method for preparing pharmaceutical dosages of ribavirin which reduces the amount of ribavirin dust that is produced during the manufacturing process, allows for greater control of dissolution rates, and increases flow rates. This goal is accomplished through a wet granulation process that combines ribavirin with specific disintegrants, binders, fillers, and wetting agents in sufficient quantities to form an extrudable mass.

One preferred embodiment of the invention teaches that the extrudable mass is mixed to form a uniform mixture of active drug and excipients, which mixture is subsequently formed into pellets by extrusion and spheronization.

More specifically, the present invention is a process for producing ribavirin pellets, comprising the steps of mixing ribavirin with at least one excipient into a uniform mixture; forming said uniform mixture into a granulated mass by adding a wetting agent to said uniform

mixture; shaping said granulated mass into flowable particles; and drying said flowable particles, resulting in dried flowable particles.

These objects, as well as other objects and advantages of the present invention, will become apparent from the following description, in reference to the illustrations and charts appended hereto.

BRIEF DESCRIPTION OF THE DRAWINGS

For a better understanding of the invention, refer to the accompanying chart in which Figure 1 is an electronic photograph of pellets produced by the preferred embodiment enlarged at a ratio of 1:1000.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention discloses a process for making pharmaceutical dosages of ribavirin through wet granulation. There are several formulas that can be utilized to produce ribavirin pellets by wet granulation, preferably with extrusion and spheronization.

Table 1

Formulation Ingredient	% Range of Total Formulation	Function in the Formulation
ribavirin	31 – 35	Active Pharmaceutical Ingredient
microcrystalline cellulose	27 – 35.5	Binder / Diluent
croscarmellose sodium	0 – 3	Disintegrant
polyethylene glycol	11 - 39	Binder / Wetting Agent

Under one of the preferred embodiments, the dry ingredients listed in Table 1 above are mixed together and granulated with the wetting agent, extruded through a screen (0.4 millimeter ("mm") to 1.0mm), spheronized, and fluid bed dried. Depending on the dosage required, the resulting pellets are filled into hard gelatin capsules sizes "1" to "00".

Table 2

Formulation Ingredient	% Range of Total Formulation	Function in the Formulation
ribavirin, U.S. Pharmaceutical Grade ("USP")	41 – 67	Active Pharmaceutical Ingredient
microcrystalline cellulose	24 – 33	Binder / Diluent
croscarmellose sodium	2 – 6	Disintegrant
polyethylene glycol	5 - 17	Binder / Wetting Agent
povidone	1 – 4.5	Binder
water USP	15 – 30 (calculated on a wet basis)	Wetting Agent

Under another preferred embodiment, the dry ingredients listed in Table 2 above are mixed together and granulated with the wetting agent, extruded through a screen (0.4mm to 1.0mm), spheronized, and fluid bed dried. Depending on the dosage required, the resulting pellets are filled into hard gelatin capsules sizes "1" to "00".

Table 3		
Formulation Ingredient	% Range of Total Formulation	Function in the Formulation
ribavirin USP	41 – 67	Active Pharmaceutical Ingredient
microcrystalline cellulose	24 – 33	Binder / Diluent
croscarmellose sodium	2 – 6	Disintegrant
povidone	1 – 4.5	Binder
lactose	5 – 10	Diluent
water USP	15 – 79 (calculated on a wet basis)	Wetting Agent

Under another preferred embodiment, the dry ingredients listed in the Table 3 above are mixed together and granulated with the wetting agent, extruded through a screen (0.4 mm – 1.0 mm), spheronized, and fluid bed dried. Depending on the dosage required, the resulting pellets are filled into hard gelatin capsules sizes "1" to "00".

One of the preferred embodiments results in a product that is encapsulated in size "1" or "1el" (elongated) capsules to form a 200 milligram ("mg") dose of active ribavirin. The total capsule weight is approximately 270 mg. One of the preferred embodiments also calls for a 200 mg pharmaceutical dosage in which at least 90% of the ribavirin dissolves within 30 minutes. Thus, although the method described in the claims can be used to produce ribavirin in different sized capsules or having different dissolution rates, this disclosure will only provide the detailed

weights and other measurements that will result in a capsule containing 200 mg of active ribavirin having the previously mentioned rate of dissolution.

In the aforesaid preferred embodiment, the following formulation and material quantities are used most preferably:

Table 4						
Ingredient	% of Formulation	mg / Capsule	kilogram ("kg")/ 10,000 Capsules 200mg (size 1el)	kg / 10,000 Capsules 300mg (size 0)	kg / 1,000,000 Capsules 200mg (size 1el)	kg / 1,000,000 Capsules 400mg (size 00)
ribavirin USP	74	200	2	3	200	400
microcrystalline cellulose	15.6	42	0.42	0.63	42	84
croscarmellose sodium	3.7	10	0.1	0.15	10	20
povidone	1.1	3	0.03	0.045	3	6
lactose	5.6	15	0.15	0.23	15	30
water USP			1.75	2.63	165	330
Total	100	270	2.7	4.05	270	540
Total with Water USP			4.45	6.68	435	870
% Water USP in the wet granulation			39	39	38	38

Ribavirin USP is mixed for 3 to 15 minutes along with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and povidone K 27-33 in a suitably sized granulator. Purified water USP is added to the mixture at a rate of 2 kg to 50 kg per minute. The wet mass is granulated for an additional 30 seconds to 20 minutes (depending on batch size).

After granulating, the wet mass is fed into an extruder at a rate that avoids product stagnation and excessive accumulation. The extruded mass is spheronized on an appropriately sized marumerizer or equivalent equipment using typical parameters. Typical parameters used during said spheronization include those listed as follows:

Jacket water temperature	45-60°C
Groove plate configuration	Medium
Marumerizer speed setting	0.5-1.0
Spherionization time	0.5-2 minute/portion

In the aforesaid preferred embodiment, the pellets are fluid-bed dried.

Drying is continued until the pellets having a loss on drying (LOD) of not more than 5% and not less than 0.5% is achieved. Following drying, the pellets are sieved by use of a 16 mesh or 18 mesh screen.

After the pellets are sieved, said pellets can be used to fill a capsule employing standard encapsulators. In this preferred embodiment, the capsule is a size 1 elongated capsule which will have a desired total capsule fill weight of 270 mg.

Said preferred embodiment produces a dosage in which at least 90% will dissolve in 30 minutes. However, it is anticipated within this application that future uses of ribavirin may lead to a demand for ribavirin dosages having a different dissolution profile. Therefore, this invention discloses and claims the addition of coatings to the dried pellets to yield other dissolution profiles. Coatings in common use include polymethacrylic, dyethyl-aminophyl, polyethanene glycols and other excipients well known in the art.